TNF alpha inhibitors in Alzheimer's disease: a systematic review

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Abstract

OBJECTIVES

The objective of this study was to evaluate the effect of tumor necrosis factor-alpha inhibitors (TNF-αI) on Alzheimer's disease (AD)-associated pathology.

DESIGN

A literature search of PubMed, Embase, PsychINFO, Web of Science, Scopus and the Cochrane Library databases for human and animal studies that evaluated the use of TNF-αI was performed on 26th October 2016.

RESULTS

The main outcomes assessed were cognition and behaviour, reduction in brain tissue mass, presence of plaques and tangles, and synaptic function. Risk of bias was assessed regarding blinding, statistical model, outcome reporting and other biases. Sixteen studies were included, 13 of which were animal studies and 3 of which were human. All animal studies found that treatment with TNF-αI leads to an improvement in cognition and behaviour. None of the studies measured change in brain tissue mass. The majority of studies documented a beneficial effect in other areas, including the presence of plaques and tangles and synaptic function. The amount of data from human studies was limited. Two out of 3 studies concluded that TNF-αI are beneficial in AD patients, with one being an observational study and the latter being a small pilot study, with a high risk of bias.

CONCLUSION

It was concluded that a large scale randomised controlled trial assessing the effectiveness of TNF-αI on humans is warranted.

The role of neuroinflammation in AD

Almost three decades ago, McGeer and colleagues noted the association between anti-inflammatory drugs and reduced risk for developing Alzheimer's disease (AD) (McGeer, Rogers, McGeer & Sibley,1990). Subsequent studies led to identification of large numbers of immune cells found in the proximity of senile plaques and neurofibrillary tangles, the histological lesions characteristic for AD (Eldik et al. 2016).

The presence of Aβ deposits in the brain can lead to the activation of an immune response and the recruitment of glial cells. In response to toxic Aβ deposits, microglia undergo morphological and functional changes to neutralise them (Olabarria, Noristani, Verkhratsky & Rodriguez, 2010). As glial cells are unable to remove the debris, their function becomes altered in a way that they actively contribute to inflammation (Bronzuoli et al. 2016).

Recent identification of genes associated with susceptibility to Alzheimer's disease provided basis for establishing the first non-descriptive link between inflammatory processes and development of AD pathology (Heppner, Ransohoff, Becher, 2015). Mutations in genes coding for triggering receptor expressed on myeloid cells 2 (TREM2) and myeloid cell surface antigen CD33 lead to a significantly increased risk of AD through impaired induction of inflammatory processes (Bradshaw et al., 2013; Jonsson et al. 2013)

Furthermore, studies on transgenic mice demonstrated that experimental induction of neuroinflammation initiated by administration of lipopolysaccharide (LPS) leads to an increase in amyloid beta deposition (Sheng et al., 2003; Lee et al., 2008).

It has been demonstrated that TNF-α can potentiate the astroglial response, driving the neuroinflammatory process (Hensley, 2010). TNF-α along with interleukin-1β and interferon-γ can induce the cleavage of the amyloid precursor protein (APP) by gamma-secretase via activation of the mitogen activated protein kinases (MAPK) pathway (Liao et al. 2004). TNF-α is also capable of stimulating the NF-$\kappa\beta$ signalling that results in an increase in the production of amyloid beta (Aβ) (Chen et al. 2012).

Thus, an increasing amount of evidence suggests that modulation of inflammation through targeting TNF-α may be a potential therapeutic strategy for AD.

TNF- αI

TNF-alpha is a powerful cytokine involved in the chronic inflammatory response (Akiyama, et al., 2000). Tarkowski et al. (2003) revealed a 25-fold difference in the levels of TNF-alpha in patients with AD compared to controls. Increasing evidence for the role of TNF-αI in alleviating AD-related pathology prompted the first administration of Etanercept for primary progressive aphasia (Tobinick, 2008). Significant cognitive benefits were observed following the first dose of treatment. The results of this study suggested that TNF-alpha may play a pivotal role in the pathology of AD and exemplified its potential as a new therapeutic target.

Aims and objectives of the current review

Previous non-systematic reviews have reported on the mechanism of action of TNF-αI and the possible benefits of TNF-alpha downregulation in AD (Cheng et al., 2014; McCaulley and Grush, 2015). The previous reviews explored the effects of Etanercept, Infliximab, Pentoxifylline and Thalidomide on AD pathology, with little critical appraisal. To the authors' knowledge, no systematic review of studies investigating the role of TNF-alpha in the pathogenesis of AD has been published. Thus, the objective of the current review was to conduct a systematic and critical analysis of the available evidence from both animal and human studies to establish whether targeting TNF-alpha is a feasible strategy for the treatment of AD and whether this class of drugs has a potential to be tested in a large-scale human trial. Four main categories of outcomes were focused on: cognition and behaviour, reduction in brain tissue mass, presence of plaques and tangles, and synaptic function. Neuropathological features were the main focus of treatment as they are the main trigger of the chronic inflammatory response seen in these individuals (Zotova, Nicoll, Kalaria, Holmes, & Boche, 2010). It was beyond the scope of this review to investigate the effect of TNF-αI on inflammation markers.

METHODS

Literature search

Six databases (PubMed, Embase, PsychINFO, Web of Science, Scopus and the Cochrane Library) were searched on 26th of October 2016 using the following search terms: (etanercept OR infliximab OR adalimumab OR certolizumab OR

golimumab OR pentoxiflylline OR "tumor necrosis factor inhibitor" OR "TNF inhibitor" OR "tumour necrosis factor inhibitor" OR "tumour necrosis factor-alpha inhibitor" OR "TNF-alpha inhibitor") AND (dement* OR alzheim* OR "cognitive decline" OR "cognitive dysfunction" OR "cognitive impairment" OR "cognitive deficit" OR "memory decline" OR "memory dysfunction" OR "memory impairment" OR "memory deficit" OR "neuropsychological test"). Etanercept, infliximab, adalimumab, certolizumab, golimumab, pentoxiflylline are TNF-αI currently used for the treatment of rheumatoid arthritis (RA).

Inclusion/exclusion criteria

Studies were included if they met the following criteria: (1) published in a peer-reviewed journal without any language restrictions; (2) report original work; (3) conducted on animal subjects or human participants; (4) the intervention had to include an administration of a TNF-αI or a genetic intervention leading to ablation of the TNF receptor (TNFR); (5) animal studies had to include transgenic or non-transgenic models of AD; and (6) human participants had to be diagnosed with AD. Conference proceedings, case studies, research protocols and unpublished dissertations or theses were excluded. In addition, studies on cell cultures were excluded.

Screening and data extraction

Studies were blindly and independently screened by two raters (JE and GR). Initially, titles and abstracts were screened and then full-text articles were retrieved for all potentially relevant studies. Discrepancies were resolved through discussion with an independent reviewer (RG). Two raters (JE and GR) blindly and

independently extracted data on study characteristics, methodology of the study and outcomes with respect to neuropsychiatric and neurohistopathological findings (as outlined in the Introduction). Again, any discrepancies were resolved through discussion with an independent reviewer (RG).

Quality assessment of methodology

The methodological quality of studies was assessed to identify potential biases, confounding factors and any errors that could affect the interpretation of the results. There is no agreed instrument for assessing methodology and risk of bias in animal studies (Krauth, Woodruff, & Bero, 2013). Consequently, a quality assessment tool was developed for the purposes of this review based on criteria proposed by Krauth, Woodruff & Bero (2013). Some of the criteria were unique to animal studies and allowed for the measurement of bias, reporting and methodological issues. The EPHPP Quality Assessment Tool (Effective Public Health Practice Project, 2009) was used for human studies as it can be applied to all study designs. The quality of studies was evaluated in the following categories: selection bias, study design, confounder, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and statistical analysis (see Appendix E). The methodological quality of included studies was assessed by two blind, independent raters (JE and GR), with any discrepancies in ratings being resolved through discussion with an independent reviewer (RG).

Identification and Characteristics of Included Studies

As shown in Figure 1, 1038 potentially relevant studies were initially identified, from which 477 duplicates were removed, yielding a total of 561 potentially relevant studies. After initial screening of titles and abstracts, 526 studies were excluded. This resulted in the extraction of 35 full-text articles, 16 of which met the inclusion criteria.

<u>Study characteristics</u>

Animal studies

Thirteen animal studies assessing the potential use of TNF-αI in the treatment of AD were identified (see Appendix A for detailed characteristics) (Cavanagh, et al., 2016) (Detrait, Danis, Lamberty, & Foerch, 2014) (Gabbita, et al., 2012) (He, Cheng, Staufenbiel, Li, & Shen, 2012) (Kim, et al., 2016) (McAlpine, et al., 2009) (Medeiros, et al., 2007) (Medeiros, et al., 2010) (Montgomery, et al., 2011) (Roerink, et al., 2015) (Russo, et al., 2012) (Shi, et al., 2011) (Tweedie, et al., 2012). The studies were very heterogenous. Transgenic mice were subjects in 9 out of 13 studies (Cavanagh, et al., 2016; Gabbita, et al., 2012; He, Cheng, Staufenbiel, Li, & Shen, 2012; McAlpine, et al., 2009; Medeiros, et al., 2007; Medeiros, et al., 2010; Montgomery, et al., 2011; Shi, et al., 2011; Tweedie, et al., 2012).Three studies used non-transgenic mice (Detrait et al., 2014; Kim, et al., 2016; Russo, et al., 2012) and one was conducted on rats as well as transgenic mice (Tweedie, et al., 2012). The most common transgenic model of AD was 3xTg-AD type and was used in four studies (Gabbita, et al., 2012; McAlpine, et al., 2009;

Montgomery, et al., 2011; Tweedie, et al., 2012). Aβ injections were used in five studies to induce similar changes to those seen in AD (Detrait et al., 2014) (Kim, et al., 2016; Medeiros, et al., 2007; Medeiros, et al., 2010; Russo, et al., 2012). The number of animals was unreported in the majority of studies. Only three of them stated this number, which ranged from nine to twenty-two (Roerink, et al., 2015; Shi, et al., 2011; Tweedie, et al., 2012). Consequently, it was not possible to calculate effect sizes. The most frequently used type of TNF-αI was 3,6'-dithiothalidomide, administered in three studies (Gabbita, et al., 2012; Russo, et al., 2012; Tweedie, et al., 2012). The methods of drug delivery included intraperitoneal, intracerebroventricular, subcutaneous injections and stereotactic infusion. Peripheral administration via an intraperitoneal injection was the most common intervention, used in seven studies (Gabbita, et al., 2012; He et al., 2012; McAlpine, et al., 2009; Medeiros, et al., 2010; Russo, et al., 2012; Shi, et al., 2011; Tweedie, et al., 2012). The length of treatment ranged from one to 90 days. One paper did not report the duration of intervention (Montgomery, et al., 2011).

Human studies

Three studies on humans were identified (see Appendix B for detailed characteristics and Appendix C for inclusion/exclusion criteria), which were heterogeneous in a number of areas. The types of study design included a randomised double-blind controlled trial (Butchart, et al., 2015), nested case-control study (Chou, Kane, Ghimire, Gautam, & Gui, 2016) and a prospective, single centre, open-label pilot study (Tobinick et al., 2006). The number of participants ranged from 15 to 325. With respect to diagnosis, standard clinical criteria were used to diagnose AD in two studies (Butchart, et al., 2015; Tobinick et al., 2006)

and both RA and AD in one study (Chou et al., 2016). Where reported, the age of participants ranged from 18 to 94 years, with the mean age ranging from 72.4 to 76.7 years (Butchart, et al., 2015; Tobinick et al., 2006). The mean Mini–Mental State Examination (MMSE) score in two out of three interventional studies that provided these data was similar: 18.2 and 20.3 (Butchart, et al., 2015; Tobinick et al., 2006). All studies recruited participants of both sexes: the mean percentage of female participants was 60%.

Administration of etanercept was the primary intervention in two out of three studies (Tobinick et al., 2006; Butchart, et al., 2015). Chou et al. (2016) carried out an observational study that aimed to determine the relative risk of AD in a cohort of patients receiving TNF-αI for RA in comparison with RA individuals without AD. In the study by Tobinick et al. (2006), etanercept was administered perispinally, in contrast to the study by Butchart et al. (2015) which involved a subcutaneous injection. Butchart et al. (2005) failed to report the details of the process of participant recruitment. The study carried out by Tobinick et al. (2006) recruited individuals from the community. Chou et al. (2016) performed a search in the Verisk Health claims database to obtain a cohort of participants with a diagnosis of AD and RA and RA only as a control. Patients received treatment for 6 months in the studies carried out by Tobinick et al. (2006) and Butchart et al. (2005). The length of treatment could not be determined in the study by Chou et al. (2016) due to its retrospective study design.

Quality Assessment

Animal Studies

Ratings of the methodological quality of included animal studies are provided in Appendix D. Only two studies reported that treatment was allocated randomly (Shi, et al., 2011; Detrait et al., 2014). These studies also explicitly stated that the investigator involved in the experiment was blinded to the intervention (Shi, et al., 2011) (Detrait et al., 2014). Blinding was only partially described in three studies (He et al., 2012) (Kim, et al., 2016) (Russo, et al., 2012). None of the studies provided information on how the number of study animals was calculated. The requirement for compliance with the Animal Welfare Act was met by all studies. Four studies declared no financial conflict of interest (Cavanagh, et al., 2016) (Detrait et al., 2014) (Roerink, et al., 2015) (Shi, et al., 2011). The statistical methods used to analyse the results obtained were partially adequate (Cavanagh, et al., 2016) (Kim, et al., 2016) (Medeiros, et al., 2007) (Montgomery, et al., 2011) (Shi, et al., 2011) (Russo, et al., 2012) or fully explained (Detrait et al., 2014) (Gabbita, et al., 2012) (He et al., 2012) (McAlpine, et al., 2009) (Tweedie, et al., 2012) (Medeiros, et al., 2010) in all studies, except one (Roerink, et al., 2015). The presence of any comorbidities in test animals was not reported in any of the studies. All of the studies provided partial information on the characteristics of the animal used, such as species, strain, genetic background, supplier, sex and weight. None of the studies, however, reported enough detail to fully meet this criterion. No mention was made in any of the studies as to whether the dose-response pattern was suitable to address the hypothesis. All of the included studies failed to report if any animals had been withdrawn from the experiment before its completion. The

time window for assessing the outcome of the experiments was rated as adequate in twelve out of thirteen studies (Cavanagh, et al., 2016) (Detrait et al., 2014) (Gabbita, et al., 2012) (He et al., 2012) (Kim, et al., 2016) (McAlpine, et al., 2009) (Medeiros, et al., 2007) (Medeiros, et al., 2010) (Roerink, et al., 2015) (Russo, et al., 2012) (Tweedie, et al., 2012).

Human Studies

Ratings of the quality of human studies are listed in Appendix E. The participants in the study by Butchart et al. (2015) were likely to be representative of the target population. There was a partial risk of selection bias in the study by Chou et al. (2016) and Tobinick et al. (2006). Two out of three studies were randomized and the study design was rated as adequate (Butchart, et al., 2015) (Tobinick et al., 2006). The study by Chou et al. (2016) was a retrospective case control analysis (Chou et al., 2016). The confounding factors were well-controlled in one study (Butchart, et al., 2015). It is unclear whether participants of the two remaining studies were exposed to any factors that may have affected the results (Chou et al., 2016) (Tobinick et al., 2006). Blinding was adequate in only one study (Butchart, et al., 2015) and partially adequate in the two remaining ones (Chou et al., 2016) (Tobinick et al., 2006). The data collection methods were valid and reliable in all studies. Any withdrawals or drop-outs were appropriately reported in two studies (Butchart, et al., 2015) (Tobinick et al., 2006). The integrity of the intervention was adequate in the study by Chou et al. (2016) and partially adequate in Butchart et al. (2015) The study by Tobinick et al. (2006) was a pilot study hence the intervention integrity was rated as inadequate.

Results of included studies

The findings in each subcategory are discussed below (see Appendix F for a summary of the key outcomes).

Cognition and behaviour

In all studies that assessed changes in cognition and behaviour, the effect of TNF-αI was beneficial. Cavanagh et al. (2016) showed that an increase in hippocampus-dependent synaptic function, an early pathological sign of AD, can be reversed by an administration of XPro1595.

Aβ-associated cognitive deficits in mice were also diminished by a subcutaneous injection of the TNF receptor 2 fused to a fragment crystallisable (Fc) domain used clinically for the treatment of RA (Detrait et al., 2014). The animals showed a dose-related response in alternation percentage in the Y-maze, with a complete reversal of cognitive deficits at 30mg/kg (Detrait et al., 2014).

Changes in exploration of the radial arm on administration of 3,6'-dithiothalidomide, but not thalidomide, in 3xTg mice were observed in one experiment (Gabbita, et al., 2012). Consistent with previous findings, 3,6'-dithiothalidomide was found to ameliorate the cognitive deficits induced by an injection of A$\beta_{1\text{-}42}$.

Kim et al. (2016) injected mice with A$\beta_{1\text{-}42}$ and performed a novel object recognition test after administration of Infliximab. Results showed that the drug counteracted the A$\beta_{1\text{-}42}$ memory impairment (Kim, et al., 2016). Tweedie et al. (2012) provided further evidence for the beneficial effect of 3,6'-dithiothalidomide-treated on cognition and

demonstrated that it is capable of decreasing levels of phosphorylated tau (Tweedie, et al., 2012).

Medeiros et al. (2007) investigated the effect of $A\beta_{1-40}$ injection on TNFR1 knock-out and iNOS-knock out mice. It was found that genetic and pharmacological inhibition of these signaling pathways ameliorated learning and memory deficits in AD-mice models.

Another study revealed that treatment with a COX-2 inhibitor and AbTNF-alpha in 57Bl/6 and TNFR1 knockout mice prevented cognitive decline and led to an improvement in spatial learning deficits (Medeiros, et al., 2010).

Reduction in brain tissue mass

None of the studies investigated the effect of TNF-αI on brain tissue mass.

Presence of plaques and tangles

Although the majority of included animal studies reported a reduction in the quantity of neuropathological features, the results were not fully consistent. Gabbita et al. (2012) showed no differences in the number of 6E10 positively stained cells in the hippocampus on thalidomide and 3,6'-dithiothalidomide administration (Gabbita, et al., 2012). Contradicting results were obtained from a different study, which not only showed a decrease in the number of 6E10+ cells, but also in the total levels of $A\beta$ (He et al., 2012). Western blotting performed on tissue samples from both thalidomide-treated and non-treated mice demonstrated a decrease in the activity of a β secretase, BACE1 (He et al., 2012) (O'Brien & Wong, 2011).

McAlpine et al. (2009) investigated the effect of short- and long-term inhibition of TNF-alpha signaling on the amyloid plaque burden in lipopolysaccharide (LPS-challenged mice. The first method involved inhibition of TNF signaling for a period of one month using XENP345, while the lentivirus-based approach blocked the pathway for a period of at least one year. A significant decrease in the number of 6E10-immunoreactive cells in the hippocampus of XENP345-treated and the lentivirus-infected mice was seen (McAlpine, et al., 2009).

A semi-quantitative analysis of brain samples from APP/PS1 mutants following an injection with Infliximab demonstrated a 40-60% decrease in $A\beta$ deposits as well as a reduction in levels of hyperphosphorylated tau (Shi, et al., 2011).

Synaptic function

Despite increasing evidence for synaptic dysfunction in AD, only three out of thirteen studies investigated this process. Cavanagh et al. (2016) assessed the effect of XPro1595 on synaptic deficits in transgenic mice. An overall enhancement of synaptic function in pre-plaque animals was observed. A study on 3xTg-ADxTNG-RI/RII knock-out mice confirmed the findings that synaptic dysfunction appears before the onset of pathology in animal models of AD (Cavanagh et al. 2016). Electrophysiological properties of tissue samples from mice injected with $A\beta$ demonstrated that $A\beta_{1\text{-}42}$ hinders the process of long-term depression. This effect was reversed following the administration of Infliximab (Kim et al., 2016).

<u>Human Studies</u>

The included human studies investigating the link between TNF-αI and the risk of AD only assessed changes in cognition and behaviour (see Appendix G for a summary of the key outcomes). Butchart et al. (2015) conducted a double-blind study with patients with mild to moderate AD to determine the tolerability and safety of etanercept. There were 20 participants in the etanercept group, and 21 in the placebo group. Adverse events were less common in the etanercept group (42 events) compared with the control group (55 events); however, this difference was not statistically significant. The nested case-control analysis performed by Chou et al. found a negative association between the use of etanercept and the risk of AD. Although this study did not examine the effect of TNF-αI on any of this review's main outcomes, it was included as it provides additional evidence for the use of TNF-αI in AD. Tobinick et al. (2006) conducted a prospective, single-centre pilot study that recruited 15 patients within the residing community. The participants were administered a weekly dose of Etanercept for six months. The results of the study demonstrated a significant difference between the etanercept and placebo group in MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and Severe Impairment Battery (SIB) over six months (Tobinick et al., 2006).

DISCUSSION

The main findings of this systematic review will be summarized below and compared with the findings of previous reviews. The clinical and research implications and strengths and limitations of the current review will also be discussed.

Previous findings

Evidence from animal studies presented in this review supports the mechanism underlying the use of TNF-αI in ameliorating AD pathology, as described by Cheng, Shen, & Li, (2014). A wider range of TNF-αI were explored in the current systematic review in comparison with the aforementioned narrative review (Cheng et al., 2014), and so the potential of this class of drugs might have been previously underestimated. Consistent with the findings of McCaulley and Grush (2015), TNF-αI were found to have a beneficial effect in patients with AD in the current review. However, a more detailed analysis conducted in the current review compared to the previous narrative review (McCaulley & Grush, 2015) revealed many flaws in the quality and significance of existing data.

Research implications

The role of the TNF signaling pathway has been a subject of many other studies, some of which may have therapeutic implications for AD patients. The evidence provided by Medeiros et al. (2007) suggested that TNF-alpha might promote the expression of inducible nitric oxide synthase (iNOS) in the CNS, leading to a more rapid progression of the pathology. Hence, modulating the levels of TNF-alpha in parallel with iNOS could be a potential therapeutic strategy for AD (Medeiros et al., 2007).

The open-label pilot study conducted by Tobinick et al. (2006) included the administration of Etanercept, in addition to the standard medication recommended in

the treatment of AD. For this reason, the contribution of these drugs to the improvement seen in the participants of this study cannot be determined. Future studies should focus on separating the effect of TNF-αI from the already established treatment to determine their true effectiveness. The analysis of the methodological quality of the study revealed a possible conflict of financial interest (Tobinick et al., 2006). Thus, the conclusions from this study may be subject to bias and so the study should be replicated.

The results obtained from Roerink et al. (2015) contradicted the study by Tobinick et al. (2006). The perispinal injection of radiolabeled cetuximab, entanercept and anakinra showed that in eight out of nine rats the compounds were not able to cross the brain-blood barrier (BBB) (Roerink, et al., 2015). This finding suggests that high-molecular weight compounds may not be effective in the treatment of AD due to their low penetrability. The importance of molecular weight on the observable therapeutic effects has also been discussed by McCaulley and Grush (2015). Small molecular TNF-alpha modulators such as thalidomide and 3,6'-dithiothalidomide should be tested.

In the study conducted by Chou et al. (2016) the analysis period ranged from 2000-2007, with the minimum age of participants being 18 years. Hence, the drug regime might have changed substantially over this period. A case-control analysis, including more recent data should be conducted.

The route of drug administration may also play an important role in achieving the most beneficial outcome. While Butchart el al (2015) chose to administer etanercept subcutaneously, Tobinick et al. (2005) injected the drug perispinally. Future research should focus on comparing the two methods.

The effectiveness of pentoxifylline on slowing down the progress of mental deterioration in patients with a diagnosis of multi-infarct dementia has also been investigated (European Pentoxifylline Multi-Infarct Dementia [EPMID] Study Group, 1996). A significant improvement on the Gottfries-Bråne-Steen (GBS) scale was seen. However, the study reported no decline in MMSE score over a 9-month period, which might imply that patients diagnosed with AD did not participate in the trial or that the treatment period was too short. Investigating the effect of Pentoxifylline on patients with a diagnosis of AD would be desirable.

Butchart et al. (2015) used six neuropsychometric tests to assess the effect of subcutaneous Etanercept on secondary clinical outcomes. After correcting for multiple comparisons, no statistically significant differences in scores on the neuropsychometric tests were found (Butchart, et al., 2015). Based on these results, it may be suggested that a TNF-αI with different pharmacokinetic properties should be tested in a clinical trial. Evidence from a study of the effect of thalidomide, etanercept and infliximab on rat models of dementia showed that the thalidomide-treated group performed best in the Morris water maze test (Elcioglu, et al., 2015). This finding suggests that future research should investigate the effect of thalidomide on AD pathology.

Currently, only limited evidence of the effect of TNF-αI on synaptic function is available and more research in this area is required. None of the studies measured reduction in brain tissue mass. Given that this is a good indication of disease severity, future research should take this into consideration.

Clinical implications

It has been shown that an increase in synaptic function of glutamatergic neurons occurs before the development of AD pathology, subsequently leading to deleterious effects on cognition (Dickerson, et al., 2005). The administration of an TNF-αI in the study by Cavanagh et al. (2016) diminished the observed abnormalities. For this reason, treatment with TNF-αI could prove beneficial for patients in the initial stages of the disease.

Strengths and limitations

The main strengths of the review was that a broad range of studies were searched across six databases. Furthermore, extracting the information on research design and analytical methods enabled classification of the quality and impact of studies. The main limitations of the review were that it was not possible to statistically synthesize the results of the included studies as the sample size was not stated in the vast majority of them. The conclusions are therefore only descriptive and lack quantitative synthesis. Non-peer reviewed studies including posters and dissertations

were also excluded. Furthermore, grey literature sources were not included in the initial screening, which may have resulted in publication bias.

Conclusion

Despite high heterogeneity in interventions assessed and outcomes measured, it can be concluded that TNF-αI have a beneficial effect on cognition and behaviour based on evidence from animal studies of AD models. All studies, except one, showed that the administration of TNF-αI ameliorates AD-related pathology. Results from an observational study and a pilot study suggested that treatment with TNF-αI may be beneficial for patients with AD. However, due to the conflict of interest in one of the studies and small sample size, caution should be expressed when interpreting the results. Chou et al. (2016) showed that out of all therapeutic drugs for RA, only treatment with TNF-αI correlated with a decreased risk of AD. Taken together, there is sufficient data to suggest that a large scale randomized controlled trial assessing the effectiveness of TNF-αI should be conducted on humans.

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Figure 1. PRISMA flow chart

Appendix A: Key characteristics of animal studies.

Appendix B: Key characteristics of human studies.

Appendix C: Inclusion and exclusion criteria for human studies.

Appendix D: Methodological quality of animal studies.

Appendix E: Methodological quality of human studies.

Appendix F: Outcomes of animal studies.

Appendix G: Outcomes of human studies.

Appendix A: Key characteristics of animal studies.

Authors	Population	Model	Number of subject animals	Drug	Dose	Method of drug delivery	Length of treatment
Cavanagh et al. (2016)	Transgenic mice	TgCRND8	unreported	XPro1595	10mg/kg	subcutaneous	28 days
Detrait et al. (2014)	NTG	injected with $A\beta_{25-35}$ or $scA\beta_{25-35}$	unreported	Etanercept	30mg/kg	subcutaneous	once a day on days 2, 4 and 6
Gabbita et al. (2012)	Transgenic mice	3xTgAD	unreported	3,6-dithiothalidomide and thalidomide	50mg/kg	intraperitoneal	daily for 70 days
He et al. (2013)	Transgenic mice	APP23	Insufficient detail	Thalidomide	100mg/kg	intraperitoneal	daily for 90 days or 3 days
Kim et al. (2016)	NTG	injected with $A\beta_{1-42}$	unreported	Infliximab	2µg/3µl	intracerebroventricular	once in 24 hours
McAlpine et al. (2009)	Transgenic mice	3xTgAD	unreported	DN-TNF XENP345 or DN-TNF	0.1mg/kg/day	intraperitoneal	twice weekly for 28 days
Medeiros et al. (2007)	Transgenic mice	TNFR1-KO and injected with $A\beta_{1-40}$	unreported	AbTNF-α, aminoguanidine, JNK or pyrrolidine dithiocarbonate	AbTNF-α - 10ηg, aminoguanidine - 100mg/kg, JNK - 50mg/kg, or pyrrolidine dithiocarbonate - 100mg/kg	intracerebroventricular	8 days
Medeiros et al. (2010)	Transgenic mice	Injected with $A\beta_{1-40}$	unreported	AbTNFα and COX-2 inhibitor NS398	1 mg/kg of NS398 and 10ng/mice of AbTNF-alpha	intraperitoneal	twice a day for 7 days
Montgomery et al. (2011)	Transgenic mice	3xTg-ADxTNF-RI/RII KO	unreported	rAAV2	2µl	stereotactic infusion	unknown
Roerink et al. (2015)	NTG	Rats	9	cetuximab, etanercept anakinra	cetuximab - 146 kDa etanercept - 51 kDa, anakinra - 17 kDa	perispinal injection	one injection
Russo et al. (2012)	NTG	injected with $A\beta_{1-42}$	unreported	3,6-dithiothalidomide	56mg/kg	intraperitoneal	daily for 14 days to explore hippocampal progenitor cell proliferation and daily for 5 weeks to look at progenitor cell survival and generation of newly derived neurons
Shi et al. (2011)	Transgenic mice	APP/PS1	20	Infliximab	150µl	intraperitoneal	daily for three days
Tweedie et al. (2012)	Transgenic mice and Rats	3xTg-AD and LPS challenged rats	22	3,6-dithiothalidomide	LPS: 56mg/kg 3xTg-AD: 42mg/kg	intraperitoneal	LPS: 14 days 3xTg-AD: daily for 42 days

Note: Aβ = amyloid peptide; AbTNF-α= anti-TNF-α antibody; APP23= APPswedish mutation transgenic; COX-2= Cyclooxygenase 2; DN-TNF= dominant-negative tumor necrosis factor; JNK= c-Jun N-terminal kinase; kDa= kilodaltons; LPS=lipopolysaccharide; NTG= non-transgenic mice; rAAV2=recombinant adeno-associated virus serotype-2 (rAAV2); scAb = scrambled amyloid peptide; TNFR1-KO= TNF receptor 1-knockout; TNFR2:Fc= TNF receptor 2 fused to a Fc domain

Appendix B: Key characteristics of human studies.

	Study design	Number of participants	Diagnosis	Mean age [years], age range	Mean MMSE	Sex (% male)	Tx	Method of administration	Setting	Dose	Length of Tx [months]
Butchart et al. (2015)	double-blind RCT	67 screened, 41 recruited and 33 completed (N=18 in etanercept group, N=15 in placebo)	Probable AD defined by the NINCDS criteria	72.4, NK	20.0 for Etanercept, 20.3 for placebo	61	Etanercept	subcutaneous	Single-centre	50mg once weekly	6
Chou et al. (2016)	nested-case control	Identified=8,500,454 participants with RA=41,109 participants with AD=9253 total number with RA and AD=325	ICD-9 for rheumatoid arthritis (RA) and a diagnosis of AD made at least 120 days before the diagnosis of RA	76.5, ≥ 18 years	NK	30	methotrexate, prednisone, sulfasalazine, three anti-TNF agents (adalimumab, etanercept and infliximab) and an anti-CD20 agent (rituximab)	Etanercept-subcutaneous; other drugs-not stated	Commercially insured adults in the Verisk Health claims database	NK	NK
Tobinick et al. (2006)	prospective, single-centre, open-label, pilot study	15	NINCDS-ADRDA Criteria for probable AD and DSM-IV criteria for AD	76.7, 52-94	18.2	40	Etanercept	perispinal	Community	25-50mg once weekly	6

Note: AD= Alzheimer's disease; Anti-CD20= a new generation monoclonal antibody; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-9= International Statistical Classification of Diseases and Related Health Problems, Ninth Revision; MMSE= The Mini–Mental State Examination; NINCDS= National Institute of Neurological and Communicative Disorders and Stroke; NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; RA= rheumatoid arthritis; RCT= Randomised-controlled trial; Tx= treatment

Appendix C: Inclusion and exclusion criteria for human studies.

	Inclusion criteria	Exclusion criteria
Butchart et al. (2015)	Modified Hachinski Ischemic Scale score <5 points, have a standardized MMSE* score above 10 and below 27 points, have an informant spending at least 24 hours per week with the participant, and be capable of giving informed consent. Patients taking a cholinesterase inhibitor, Memantine, or antidepressant medication were required to have been on medication for a minimum period of 90 days before baseline.	Prior exposure to amyloid vaccines, monoclonal antibodies, or IV immunoglobulins for the treatment of AD*. Also patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis, or those taking anti–TNF-α agents, immunosuppressive drugs, and/or oral prednisone>10 mg/d within the past 90 days. Also participants with known contraindications (active infections) or cautions (previous significant exposure to tuberculosis, herpes zoster, hepatitis B, heart failure, demyelination disorders, and active malignancy within past 5 years to the use of etanercept.
Chou et al. (2016)	A diagnosis of RA* based on at least two outpatient claims with the same diagnosis or one inpatient claim as defined by ICD-9* for RA and a new diagnosis of AD made at least 120 days after the initial diagnosis of RA	Identifiable diagnosis of RA prior to the analysis period, claims data about RA for 6 months prior to the analysis period. During any time of the analysis period, they also had a diagnosis of inflammatory bowel disease (Crohn's disease and ulcerative colitis), psoriatic arthritis, frontotemporal dementia, Lewy body dementia, Parkinson's disease, stroke, or vascular dementia, if they had a diagnosis of AD made before the index date (i.e., diagnosis of RA) or less than 120 days after the index date. If less than 12 months of data were available for assessment of exposure to different therapeutic agents after the index date
Tobinick et al. (2006)	Patients with a clinical diagnosis of AD declining despite the clinical treatment	Active infection, multiple sclerosis (or any other demyelinating disorder), vascular dementia, clinically significant neurologic disease other than AD or a score greater than 4 on the modified Hachinski Ischemic Rating Scale, pregnancy, uncontrolled diabetes mellitus, tuberculosis, history of lymphoma, or congestive heart failure. Female participants who were premenopausal, fertile, or not on acceptable birth control; and patients with a white blood cell count < 2500 cells/mm3, hematocrit < 30, or a platelet count < 100,000 cells/mm3. Study eligibility also required the dose of all central nervous system-active medications to be unchanged in the 4 weeks before study initiation and during the entire course of the clinical trial.

Note: AD=Alzheimer's Disease, ICD-9= The International Classification of Diseases, MMSE=The Mini–Mental State Examination; Ninth Revision; RA=rheumatoid arthritis TNF-α=Tumour Necrosis Factor- α;

Appendix D: Methodological quality of animal studies.

Study	Random allocation of treatment	Blinding	Inclusion and exclusion criteria stated	Sample size calculation	Compliance with animal welfare requirements	Conflict of interest disclosed	Statistical model explained	Animals with comorbidity	Test animal details	Dose-response model	Every animal accounted for	Optimal time window used
Cavanagh et al. (2016)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Adequate	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Detrait et al. (2014)	Adequate	Adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate	Adequate	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Gabbita et al. (2012)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
He et al.	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Kim et al.	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
McAlpine et al. (2009)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Medeiros et al.	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Medeiros et al 2010.	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Montgomery et al. (2011)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Roerink et al. (2015)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Adequate	Inadequate/ unreported	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Partially adequate	Adequate
Russo et al. (2012)	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate
Shi et al. (2011)	Adequate	Adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate	Adequate	Partially adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported
Tweedie et al. (2012)	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Inadequate/ unreported	Adequate	Inadequate/ unreported	Adequate	Inadequate/ unreported	Partially adequate	Inadequate/ unreported	Inadequate/ unreported	Adequate

Appendix E: Methodological quality of human studies.

	Selection bias	Study design	Confounder	Blinding	Data collection methods	Withdrawals and drop-outs	Intervention integrity
Butchart et al. (2015)	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Partially Adequate
Reason	1. Individuals somewhat likely to be representative of the target population 2. 80-100% of selected individuals agreed to participate	1. Study design: RCT 2. Study randomised 3. Method of randomisation described 4. Method of randomisation was appropriate	1. There were no important inter-group differences prior to the intervention 2.	1. Outcome assessor unaware of the intervention or exposure status of participants 2. Participants unaware of the research question	1. Data collection tools were valid 2. No information regarding the reliability of data collection tools	1. Withdrawals and drop-outs were reported in terms of numbers and/or reasons per group 2. 80-100% of participants completed the study	1. 80-100% of participants received the allocated intervention or exposure of interest 2 Consistency of intervention was not measured 3. Unlikely that subjects received an unintended intervention
Chou et al. (2016)	Partially Adequate	Partially Adequate	Inadequate or unclear	Partially Adequate	Adequate	Partially Adequate	Adequate
Reason	1. Individuals somewhat likely to be representative of the target population 2. Retrospective study	1. Study design: case-control 2. Study not randomised	1. No information regarding inter-group differences 2. No information regarding the control of relevant confounders	1. No information regarding the assessors 2. Participants unaware of the research question	1. Data collection methods were valid 2. Data collection methods were reliable	Cannot comment on withdrawals and drop-outs due to the retrospective nature of the study	
Tobinick et al. (2006)	Partially Adequate	Adequate	Inadequate or unclear	Partially adequate	Adequate	Adequate	Inadequate or unclear
Reason	1. Individuals somewhat likely to be representative of the target population 2.. 80-100% of selected individuals agreed to participate	1.Study design: controlled clinical trial 2. Study not randomised	1. No information regarding inter-group differences 2. No information regarding the control of relevant confounders	1. Outcome assessor unaware of the intervention or exposure status of participants 2. No information regarding the extent of information given to study participants	1. Data collection methods were valid 2. Data collection methods were reliable	1. Withdrawals and drop-outs were reported in terms of numbers and/or reasons per group 2. 80-100% of participants completed the study	1. 80-100% of participants received the allocated intervention or exposure of interest 2 Consistency of intervention was not measured 3. No information regarding the possibility of unintended interventions

Appendix F: Outcomes of animal studies.

	Cognition and behavior	Reduction in brain tissue mass (atrophy)	Presence of tangles and plaques	Synaptic Function	Other findings
Cavanagh et al. (2016)	Increase in latency in all XPro1595-treated mice (p<0.001). A significantly lower latency than untreated mice at day 8 (p<0.05) Decreased time spent in the avoidance task in either genotype, following treatment (p<0.05)	unreported	unreported	Treatment with XPro1595 caused a significantly greater decrease in mean fEPSP slope in slices from TgCRND8 mice (p<0.001). XPro1595 (p< 0.01) abolished the increased LTP in slices from TgCRND8 mice. The input-output function in 6-month old TgCRND8 XPro1595-treated mice at a prodromal age was significantly higher than saline-treated TgCRND8 mice (p < 0.05) for the same fiber volley sizes and not significantly different than NTG controls	unreported
Detrait et al. (2014)	Administration of the TNFR2:Fc counteracted amyloid-induced decrease in alternation percentage (p<0.01) Method of assessment: inhibitory avoidance Treatment with TNFR2:Fc increased the retention latencies in a dose-dependent manner. At 10mg/kg the retention latency was increased when compared with the control group. At 30mg/kg a complete reversal of the deficit was observed	unreported	unreported	unreported	Hippocampal TNF-alpha levels doubled in mice administered with Aβ only (p<0.001). Treatment with TNFR2:Fc normalized the levels
Gabbita et al. (2012)	3,6′-dithiothalidomide prevents cognitive impairment (p<0.05)	unreported	No difference in the number of 6E10+ positive cells between the treated and control groups was found	unreported	Both Thalidomide and 3,6′-dithiothalidomide significantly inhibited BV2 TNFα production p<0.0001 and reduced LPS-induced brain cortical TNFα mRNA and protein levels to near control values p<.0001 3,6′-dithiothalidomide treatment reduces brain and spleen tumor necrosis factor-α levels, p<.05 3,6′-DT reduces TNF-α in central nervous system-infiltrating leukocytes, p<.001 3,6′-dithiothalidomide decreased TNF-α in myelomonocytic/granulocytic cells, p=.0309
He et al. (2013)	unreported	unreported	Thalidomide reduced Aβ load (p<.05) Significant decrease in 6E10-positive plaques in the neocortex and hippocampus following thalidomide administration (p<0.01)	unreported	Significant decrease in BACE1 amount with thalidomide application (p<0.05), and lower BACE1 activity (p<0.05) No significant changes of APH-1 levels, nicastrin and PS-1 with thalidomide application (p>0.05)

Study					
			In the Thalidomide-treated group the levels of insoluble Aβ1-42 and Aβ1-40 were reduced by 51% and 83%, respectively		No significant changes in the amount of NEP and ODEA expression (p>0.05)
Kim et al. (2016)	Infliximab treatment blocked Aβ1–42-induced impairment of recognition memory without affecting normal recognition memory (p=0.0113). Discrimination ratio was also restored after infliximab (p=0.0014)	unreported	unreported	ex vivo: Infliximab treatment blocked Aβ1–42-induced LTD impairment (P< 0.0001) without affecting control LTD (P = 0.0004) in vitro: Infliximab treatment blocked Aβ1–42-induced LTD impairment (P=0.0020) without affecting control LTD (P = 0.0092)	unreported
McAlpine et al. (2009)	unreported	unreported	lenti-DN-TNF-transduced brains displayed a significant (~60%) reduction in accumulation of intraneuronal APP-derived 6E10-immunoreactive protein compared to lenti-GFP transduced (p<.05) XENP345 inhibited the appearance of 6E10-positive cells in the hippocampus (p<.05) Counts in the hilar region of the hippocampus revealed that administration of XENP345 significantly reduced the appearance of 6E10-IR protein in the hilar regions of the hippocampus of the LPS-treated 3xTgAD mice compared to the saline-infused animals (p<0.05) Inhibition of TNF signaling with the DN-TNF inhibitor XENP345 (p=0.34) or with lenti-DN-TNF (p=0.15) had no effect on levels of Aβ peptides	unreported	unreported
Medeiros et al. (2007)	iNOS inhibitor AG improved the cognitive deficits during training trials, p<.0001 and test trials p<.0001 on the Morris water maze	unreported	unreported	Prevented the synaptic disruption in the CA1, p<.01, CA2 p<.01 but not in the CA3 p<.05 and parietal cortex (p>.08)	unreported
Medeiros et al. (2010)	Treatment with NS398 resulted in a significant improvement of spatial learning deficits (p<0.05 and p<0.01 compared with the PBS/vehicle treated group, p<0.05 and p<0.01 compared with the AB1-50 vehicle treated group	unreported	unreported	unreported	unreported
Montgomery et al. (2011)	unreported	unreported	unreported	3xTg-ADxTNF-RI/RII KO mice showed significantly smaller evoked fEPSPs compared with Non-Tg mice (p= 0.02)	unreported

Study					
Roerink et al. (2015)	unreported	unreported	unreported	unreported	Perispinal injection of radioactively labelled cetuximab, etanercept and anakira resulted in the accumulation of the drugs in the brain in only one out of nine animals. In that animal, the concentration of the drug was less than 0.01% of the injected dose
Russo et al. (2012)	$A\beta_{1-42}$-induced memory deficits are abolished by 3,6′-dithiothalidomide treatment, $p < .05$	unreported	3,6′-dithiothalidomide treatment attenuates the effect of $A\beta_{1-42}$ injection on hippocampal progenitor cell proliferation $p < .01$. 3,6′-DT treatment diminishes the effect of $A\beta_{1-42}$–induced inflammation on BrdU-cells survival at 4 weeks, $p < .001$	unreported	3,6′-dithiothalidomide treatment decreases microglia activation in response to $A\beta_{1-42}$ – induced neuroinflammation $p < .001$
Shi et al. (2011)	unreported	unreported	Treatment with Infliximab resulted in a decreased in the amyloid plaques of APP/PS1 transgenic mice. A reduction in tau phosphorylation levels was also reported on semi-quantitative examination	unreported	unreported
Tweedie et al. (2012)	drug-treated animals performed at a level similar to control mice in the Morris Water ($p < 0.05$)	unreported	unreported	unreported	3,6′-DT reduced LPS-induced chronic neuroinflammation and restores LPS-mediated abnormal hippocampal neuronal plasticity ($p < 0.05$)

Note: $A\beta$= amyloid beta; APH-1=anterior pharynx-defective 1; APP= Amyloid Precursor; BACE1= Beta-secretase 1; DN-TNF= dominant negative tumor necrosis factor; fEPSP=field excitatory postsynaptic potential; GFP= green fluorescent protein; iNOS= Inducible nitric oxide synthase; LTD= Long-term depression; Protein; LPS= lipopolysaccharide; NEP= neutral endopeptidase; NTG= nontransgenic; PS-1= presenilin-1;TNFR2:Fc= tumor necrosis factor receptor 2 fused to a Fc domain (TNFR2:Fc); TNF-RI/RII KO= tumor necrosis factor receptor-1 knockout,

Appendix G: Outcomes of human studies.

	Cognition and Behaviour	Other statistically significant findings
Butchart et al. (2015)	**Observed Cases** <u>Week 12</u>: no significant difference between etanercept and placebo on SMMSE (p=1.0), ADAS-cog (p=0.9), BADLS (p=0.8), NPI (p=0.2), CSDD (p=0.9), CGI-I (p=0.6) <u>Week 24</u> no significant differences on ADAS-cog (p=0.7), CSDD (p=0.4), SMMSE (p=0.07) or CGI-I (p=0.3) were seen, but a significant difference on BADLS (p=0.04) and NPI (p=0.02) **ITT-LOCF** <u>Week 12</u> no significant difference between the etanercept and placebo groups on SMMSE (p=0.9), ADAS-cog (p=0.8), BADLS (p=0.8), NPI (p=0.2), CSDD (p=0.9), CGI-I (p=0.7) <u>Week 24</u> no significant difference on SMMSE (p=0.2), ADAS-cog (p=0.5), BADLS (p=0.1), NPI (p=0.2), CSDD (p=0.6), CGI-I (p=0.8)	
Chou et al. (2016)		Only the anti-TNF agents as a group showed a significant reduction in the relative risk of AD among RA subjects following treatment (p=0.02) A significant decrease in the relative risk of AD in RA subjects following treatment was only found in the Etanercept group (p=0.03)
Tobinick et al. (2006)	A significant beneficial effect of treatment on the change in MMSE (p<0.001), ADAS-Cog (p<0.002), and SIB (p<0.001) from baseline	

Note: AD= Alzheimer's Disease; ADAS-cog= Alzheimer's Disease Assessment Scale-cognitive subscale; BADLS= The Bristol Activities of Daily Living Scale; CGI= The Clinical Global Impressions Scale; (CSDD)=The Cornell Scale for Depression in Dementia; ITT-LOCF= Intent-to-Treat Last Observation Carried Forward; SMMSE= Standardized Mini-Mental State Examination; NPI= The Neuropsychiatric Inventory